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Short communications

Use of Tc99m-nanocolloid for sentinel node identification in cervical cancer

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Abstract

BACKGROUND: The initial draining lymph node for a primary tumor is referred to as the "sentinel" node. Firstly adopted in the management of patients with cutaneous melanoma and breast cancer, it is now widely tested in cervical cancer. In patients with cervical cancer, lymph node status is the most important prognostic factor for survival. In patients with cervical cancer FIGO stage I and II pelvic lymph node metastases are expected in 0–16 and 24.5–31% and para-aortic lymph node metastases are expected in 0–22 and 11–19% of patients. The removal of pelvic and para-aortic lymph nodes is essential for assessing the biology of the disease. Lymphoscintigraphy enables the visualisation of lymphatic drainage patterns from a great variety of tumour sites prior to surgery. Therefore, the current procedure is to perform the pre-operative mapping of sentinel nodes by static and/or dynamic lymphoscintigraphy, followed by in vivo identification using a gamma detection probe and selective surgical resection.

MATERIAL AND METHODS: Between 2001–2003, 37 patients with cervical cancer FIGO stage I-IIa were deemed to be qualified to undergo lymphoscintigraphy. The day before surgery ^{99m}Tc-nanocolloid (100 MBq; 0.5–1.0 ml in volume) was applied in each quadrant of the cervix or around the tumor. The static scintigraphic scans were performed after 2 hours p.i. using a dual-head large-field-of-view Siemens gamma-camera equipped with high resolution collimators. SNs were identified intra-operatively using a handheld gamma detection probe (Navigator GPS-Tyco) and intra-operative lymphatic mapping with blue dye. After a resection of the SNs, a standard radical hysterectomy with pelvic and low para-aortic lymph node dissection was performed. Tumor characteristics were compared with sentinel node detection and with the histopathological and immunohistochemical results.

RESULTS: The scintigraphy showed a focal uptake in 35 of the 37 patients. In all women one or more sentinel lymph nodes were identified intra-operatively. Of them, 24 patients had those located bilaterally. Histologically positive SNs were found in 5 women (13.5%).

CONCLUSIONS: A combination pre-operatively administered radioactively labelled albumin with blue dye allows the successful detection of SN in patient with cervical cancer. This technique will result in a real advance in the less aggressive management of patients with early stage cervical cancer. Sentinel lymph node status may be representative of the pelvic lymph nodes status in cervical cancer and thus could provide important information for further treatment.

Key words: sentinel lymph nodes, cervical cancer, lymphoscintigraphy

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Introduction

Sentinel nodes (SNs) are defined as the first draining lymph nodes from a tumour when lymphatic metastases occur [1]. In 1977 Cabanas was the first to define the term "sentinel lymph node" and to test the concept in penile cancer [2]. He injected radiographic contrast media into the dorsal lymphatics of the penis in patients in penile carcinoma, followed by radiographic imaging of the penis. The first visualised inquinal lymph node was called the sentinel lymph node (SLN). This concept was then adopted in patients with melanoma [3–7], breast cancer [8–11] and more recently in surgery for colorectal [12] and gastric cancer [13] and in ginecology, by Lavenback and Burke for vulvar cancer [14], by Dargent et al. for cancer of the cervix.

Lymph node metastasis is one of the most important prognostic factors in patients with cervical carcinoma. Dissection of the regional pelvic lymph nodes is incorporated into the procedures for radical hysterectomy but is accompanied by significant morbidity. Lymphadenectomy increases the duration of the procedure, the amount of blood loss from vessels during surgery,

the incidence of post-operative ileus, and the risk of infection. In addition, up to 5% of patients complain of lymphedema of the thighs or legs. Pre-operative diagnosis of lymph node involvement would prevent unnecessary surgery. When the results of diagnostic procedure including lymphoscintigraphy are positive, patients could be treated with combined chemo- and radiotherapy instead of undergoing a radical hysterectomy [15].

The aim of this study was to perform pre-operative lymphatic mapping in patients with cervical cancer and then confirm the presence of sentinel nodes using a gamma detection probe and blue dye for assessing the clinical usefulness of this method and the possibility of avoiding radical hysterectomy and lymph node dissection.

Material and methods

Between years 2001–2003 lymphatic mapping and sentinel node detection were performed in 37 patients with cervical cancer FIGO stage I–IIa. 36 patients had squamous cell carcinoma and 1 patient had adenocarcinoma of the cervix. The informed consent of the patients was obtained.

The day before surgery ^{99m}Tc-nanocolloid (100 MBq, 0.5–1 ml in volume) was applied in each quadrant of the cervix or around the tumor (about 5–10 mm deep into the cervix). In all patients about 2 hours p.i. of the tracer the static scintigraphic scans were performed. This scintigraphy was detected using a dual-head large-field-of-view Siemens gamma-camera equipped with high resolution collimators. The first persistent focal accumulation which appeared was considered to be a sentinel node.

On the day of surgery, after the induction of general anesthesia, 4 ml of Patent Blue was injected into the cervix at the same location and depth as the radioisotope. The abdomen was opened by means of a midline incision, the peritoneal cavity was inspected and an incision was made in the pelvic peritoneum to expose the retroperitoneum. The retroperitonem was then visually inspected and scanned with a hand-held gamma counter (Navigator GPS) to locate the sentinel node. The pelvic and para-aortic regions were surveyed. Lymph nodes that appeared darker then other nodes or had a blue color were considered to be sentinel nodes. The radioactive lymph nodes identified with the gamma probe were removed and the radioactivity was measured ex vivo. If the counts were at least 10-fold above the background radiation levels the node was considered to be a sentinel node. All hot and/or blue nodes were dissected, sampled, and numbered for separate pathologic examinations. The operating surgeons did not attempt to dissect sentinel nodes from the surrounding fat pat. The final number of sentinel nodes was counted by a pathologist. Subsequently, a complete pelvic and, in some cases, para-aortic lymphadenectomy was performed. Sentinel nodes were submitted for hematoxylin and eosin staining and, if negative, unstained slides were prepared for cytokeratin immunohistochemical analysis (cytokeratin 19).

Results

The intra-operative detection of sentinel nodes was successful in 36 cases (97.30%). Only in one patient was the sentinel node not found. In this case, the lymph nodes exposed during surgery were enlarged, hard and creating conglomerations along external hip vessels. This patient, just like our other patients, had not undergone radiotherapy treatment. Moreover, she had no history of inflammation in the pelvic minor area/region. The mean number of sentinel nodes detected was 3.43 (range 0–7). The total number of sentinel nodes found was 119.

In 28 patients (75.68%) the sentinel nodes were blue and radioactive, in 2 cases (5.41%) only blue and in 6 cases (16.22) only radioactive. Out of 119 sentinel nodes detected, 92 (in 77.31%) were found in the region of hypogastric artery division.

The scintigraphy showed a focal uptake in 35 of the 37 patients. At least one sentinel node (hot spot) was detected in these patients. In 13 cases they were localized next to the cervix (in 6 patients unilaterally and in 7 cases bilaterally). The other cases had hot spots placed above and laterally to the cervix on the pelvic walls. Of them, in 17 cases, there were bilateral hot spots. Histologically positive SLNs were found in 5 women. One patient with metastases in the lymph nodes had a false negative sentinel node.

Four examples of sentinel nodes are presented on the Figure 1: Sentinel nodes: a) bilateral on the pelvic walls, b) bilateral next to the cervix., the Figure 2: Sentinel nodes: a) unilateral on the pelvic walls, b) unilateral next to the cervix.

Discussion

Lymphatic mapping is a promising strategy to confirm nodal status and minimize post-operative morbidity in patients with early cervical cancer. Previous investigators have described the concept during laparotomy, with blue dye during laparoscopy, or with external gamma probes after the laparoscopic removal of nodes [16–19].

Dargent et al. were able to find a blue-dyed lymph node (they injected Patent Blue Violet intracervically) after the systematic laparoscopic dissection of the pelvic sidewall in 25 of 35 patients with

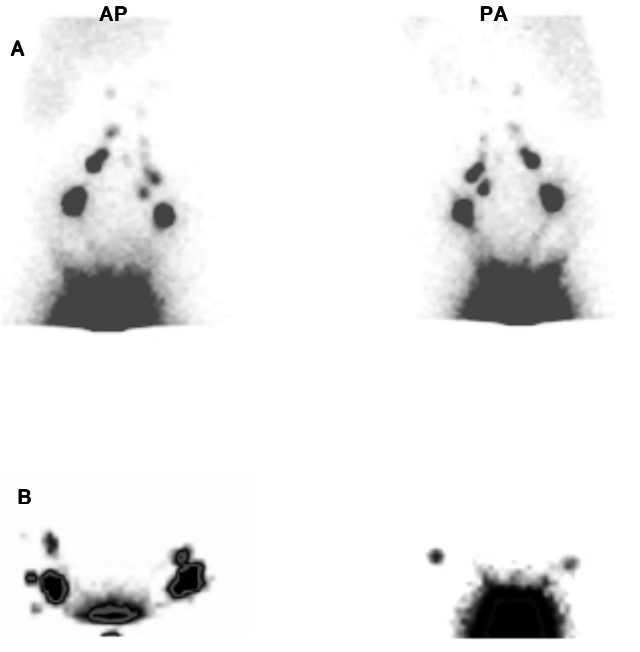

Figure 1. Sentinel nodes. **A.** Bilateral on the pelvic walls; **B.** Bilateral next to the cervix.

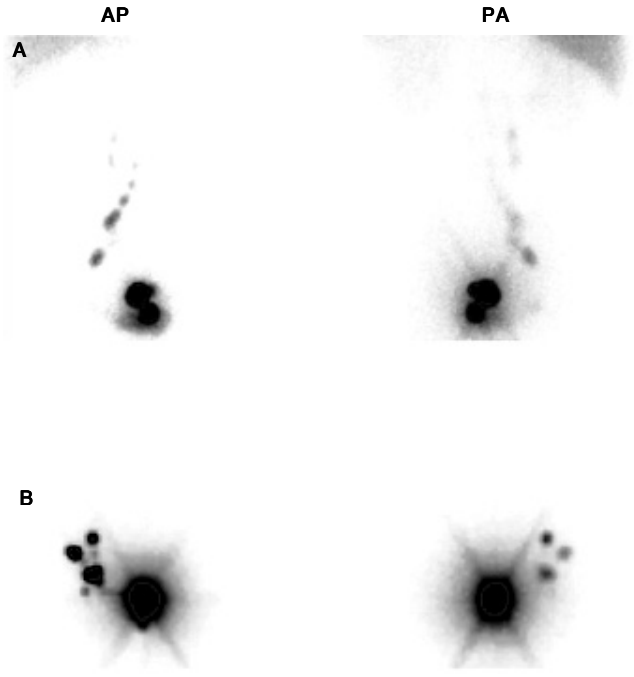

Figure 2. Sentinel nodes: **A.** Unilateral on the pelvic walls; **B.** Unilateral next to the cervix.

early cervical cancer [15, 20]. Failure to identify the sentinel lymph node was related to the quantity of injected blue dye, but not to tumor stage, prior conization or tumor volume. They found a 100% sensitivity using only blue dye injection, but the problem was the rate of false negatives [19, 20].

O'Boyle et al. identified a total of 23 SLN in 12 of 20 patients (60%) using only a patent blue dye injection. In 4 patients with metastatic nodal disease, three had tumors involving a sentinel node and the fourth had no identifiable blue-dyed node [19, 21]. The visual detection of dye uptake in lymph nodes is sometimes difficult [22]. Failure to identify SLN may be due to an insufficient quantity of injected patent blue dye [20], the disruption of lymphatic channels during dissection, or the poor operative exposure of lymphatic tissues [19, 21]. A detection rate of sentinel nodes of 78% was obtained by Malur et al. by a pre-operative injection of Albu-Res labeled with the radioactive isotope ^{99m}Tc and/or an intra-operative injection of Patent Blue Dye in a series of 50 patients with cervical cancer [15, 23]. After a combined injection of radioactivity labelled albumin and blue dye, the detection rate, sensitivity, and negative predictive values were 100% in this study. Verheyen et al. [15, 18] using a similar technique in patients with stage I B and II A cervical carcinoma in with laparoscopic lymph node dissection was followed by laparotomy and radical histerectomy and pelvic lymph node dissection. In seven out of 10 patients a sentinel node could be identified. Lavenback et al. studied 39 patients by combining a pre-operative lymphoscintigraphy with ^{99m}Tc-nanocolloid with intra-operative lymphatic mapping with isosulfan blue and a handheld gamma probe. The sensitivity of sentinel node biopsy was 87.5% while the negative predictive value was 97% [24].

Isosufan blue dye is used for dye-guided sentinel lymph node biopsy for visual detection. According to the initial experience of using only dye-guided sentinel node biopsy, the identification rates of sentinel lymph nodes ranged between 66–82% [25]. Radionuclides for lymphatic mapping should be a few hundred nanometers in size to permeate the lymphatic vessels and remain in the sentinel lymph nodes. However, technetium-99m HAS is too small (< 5 nm) to be retained in the sentinel lymph nodes and technetium-99m TC is too big (> 500 nm) to migrate through the lymphatic vessels compared with technetium-99m colloid albumin [26, 27]. These factors contributed to low success rate of sentinel node biopsy with the hand held gamma probe detector. Combining isosulfan blue dye with ^{99m}Tc colloid albumin should be used for the lymphatic mapping as this combination can improve the rate identification of SNs up to 100%, and seems to be the best way to accurately detect sentinel lymph nodes [27]. If sentinel lymph nodes are histologically negative by immediate frozen section examination, extensive pelvic lymph node dissection can be omitted. However, it may be difficult to detect the micrometastasis of cancer cells by the frozen section of SNs. To compensate for these false negatives, it would be helpful to examine multiple sections of sentinel lymph nodes especially with immunohistochemical staining [27].

In this paper, we describe a complete laparoscopic approach of SNs detection using a combination of blue dye, a hand held gamma probe and isotopic detection in patients with early stage cervical cancer. Our study shows that after an intra-cervical injection of ^{99m}Tc-nanocolloid, sentinel nodes can be detected intra-operatively in 97.3% of patients by using an endoscopic gamma probe. A combination of these techniques increases the detection rate.

On the basis of the results obtained, the concept of sentinel node seems to be true in cervical cancer. The combination of radioisotope and dye technique allowed the detection of sentinel nodes in almost all cases of cervical cancer. Pre-operative lymphoscyntigraphy enables the surgeon to ascertain the presence of sentinel nodes and their rough localization.

Sentinel node mapping (combined use of a radioisotope and blue dye injection) is a promising technique for use in patients with early stage cervical cancer, it could be considered as the final diagnostic step before applying a therapeutic plan. Sentinel lymph node biopsy is less invasive than complete pelvic lymph nodes dissection and lowers both post-operative morbidity and costs.

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